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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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Signed Andrew George

Dated 5 November 1999

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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Gwent NP9 1RH

1. Your reference: 251098

2. Patent application number *(The Patent Office will fill in this part)*: **9823446.1**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*:
ASHBY SCIENTIFIC LTD.
UNIT 11
ATLAS COURT
COALVILLE
LEICS. LE67 3FL

Patents ADP number *(if you know it)*: 673640002

If the applicant is a corporate body, give the country/state of its incorporation: ENGLAND

4. Title of the invention: IMPROVEMENTS IN BIO-REACTORS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*:
Venner Shipley & Co
20 Little Britain
London
EC1A 7DH.

Patents ADP number *(if you know it)*: 5177 205199
ca

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
~~9720611.4~~	~~30/09/97~~

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

IMPROVEMENTS IN BIO-REACTORS

This invention relates to means for the growing of animal cells, plant cells and micro-organisms ("the bio-substances"), and their use in bio-processes. Methods according to the invention are particularly applicable to the bio-processing of liquors containing particulate matter, such as blood cells or cell debris.

Bio-reactors according to prior art are normally closed systems, and as such have the disadvantages of relatively low productivity and efficiency; a particular drawback is the limited volume of oxygen available for the reaction in such closed systems. They are, moreover, not normally suitable for the processing of liquors containing particulate matter, such as whole blood.

The present invention aims to overcome or minimise the aforesaid drawbacks, and to provide a more efficient means for growing cells and subsequent harvesting of the desired product; e.g. proteins, such as antibodies etc. - ("the product").

According to a broad aspect of the invention, the liquor comprising the bio-substances is processed within an envelope, the walls of which are at least in part oxygen permeable, and wherein a surface of silicone rubber is provided to assist the growth process of the bio-substances. The product is subsequently generated in a continuous process, by passage of liquid (nutrient) medium over the bio-substances.

According to a preferred method of carrying the invention into effect; there is provided a reactor system, comprising preferably a plurality of tubular reactor envelopes ("the reactor tubes"), made at least in part of oxygen permeable material, such as non-porous silicone rubber. In the interior of the reactor tubes, coatings of surface porous or rough textured silicone rubber are provided, to constitute the support for the growth of the bio-substances. A preferred coating of this type is that known under the trade name of "TexturSil", a silicone rubber coating exhibiting a micro-cupulated surface texture; this is particularly suited to the present purpose owing to its affinity to cells and the large surface area provided through its surface texture.

According to a second aspect of the invention, apparatus is provided especially adapted for the bio-processing of liquors containing particulate matter, such as blood cells or cell debris. The continuous flow system according to the invention is especially applicable to the processing of whole blood, as in an artificial extra-corporeal organ, e.g. substituting or supporting the functions of the human liver. Notably, the system obviates the need of separating the particulate matter prior to processing and then having to re-unite the constituents.

For these purposes apparatus is provided, comprising reactor tubes as aforesaid, within which, however, are positioned co-axial tubular dialysis membranes of smaller diameter, consisting e.g. of cellulose acetate (the "dialysis tubes"). The latter are arranged to be separately connected to common inlets and outlets at the respective ends. The bio-processing operation then involves the following procedures:

(i) The cells, grown to perform the bio-processing function, are produced by the procedures described herein in respect of the preferred method, the medium being thereafter removed from the reactor tubes.

(ii) The nutrient medium is passed through the dialysis tubes, preferably in opposing direction to that of the flow of the liquor in (iii). The medium is introduced from a reservoir through the inlet at one end of the dialysis tube, issuing at the outlet on the opposing end. If desired, the medium may be recycled from the outlet, to return again to the inlet of the tubes.

(iii) The liquor to be processed (e.g. blood) is then arranged to flow through the reactor tubes (the interior carrying the surface textured silicone rubber layers now coated with cells). The liquor is introduced for this purpose at the inlet of the reactor tubes, formerly serving as the medium inlet, issuing at the outlet on the opposing end. During this procedure, nutrient from the medium passes through the dialysis membranes, traversing the stream of liquor, to feed the cells adhering to the coating of the reactor tubes; at the same time they also perform the function of cleansing the liquor of waste material (e.g. ammonia, urea etc.).

(iv) The treated liquor is finally collected at the outlet of the reactor tubes.

The accompanying Figure 3, a side cross-sectional view, illustrates by way of example only, an embodiment in accordance with the second aspect of the invention described above. For clarity, the illustration shows an assembly comprising only two reactor tubes, instead of the larger number preferred in practice. Cells are grown by the passage via inlet 9 of medium comprising the cell line, through the reactor tubes 1 carrying the surface textured silicone rubber coatings (not shown), as in the previous example. After evacuation of the liquid, the nutrient medium is passed through the dialysis tubes 12 via medium inlet 11, issuing at outlet 8. At the same time the liquor (e.g. whole blood), to undergo the bio-reaction, is passed through the reactor tubes via inlet 9, for collection at outlet 10.

According to a third aspect of the invention, in a simpler form, there is provided a reactor chamber comprising an outer envelope at least in part permeable to oxygen (e.g. non-porous silicone rubber), carrying an inner coating or layer of surface textured silicone rubber, as heretofore described. The chamber is used for the growing of bio-substances as in the previous examples. On completion, the cells are "harvested" by opening the container and flushing out the contents with the medium or by mechanical harvesting. The reactor may again be in tubular form, or it may, for example, be in the form of a (flexible) bag, e.g. of non-porous silicone rubber, carrying an interior lining or coating of the surface textured material as previously described, or it may be in other configurations, e.g. flasks or the like.

The productivity and efficiency of the growth process, especially in the case of attachment-dependent cells, can be substantially enhanced by these means, as compared with conventional reaction vessels.

Reaction vessels essentially of glass or polystyrene (so-called "roller bottles"), provided with textured interior surfaces have been described in our co-pending UK patent Patent Application No.0526032.9. These, however, differ fundamentally from the systems described here, in that glass or polystyrene containers involved in the former case are not oxygen-permeable, and as such cannot sustain the cell growth process in the manner made possible by the present invention.

Figure 1

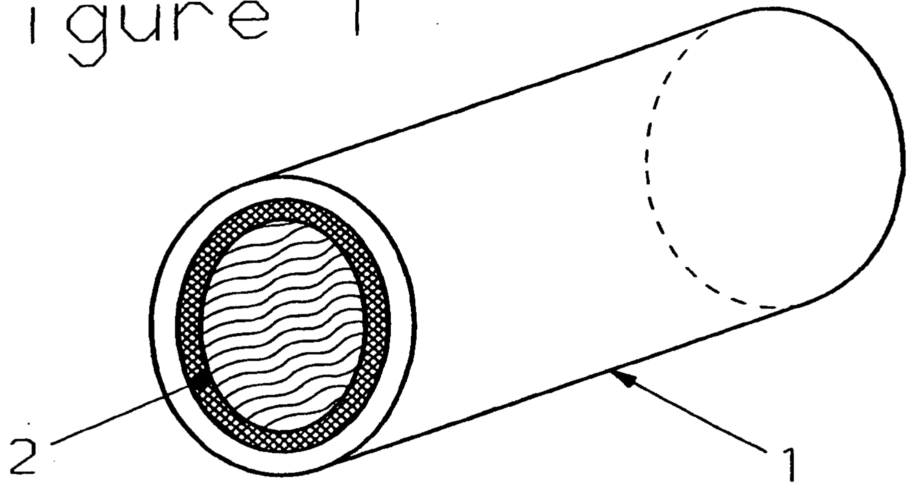


Figure 2

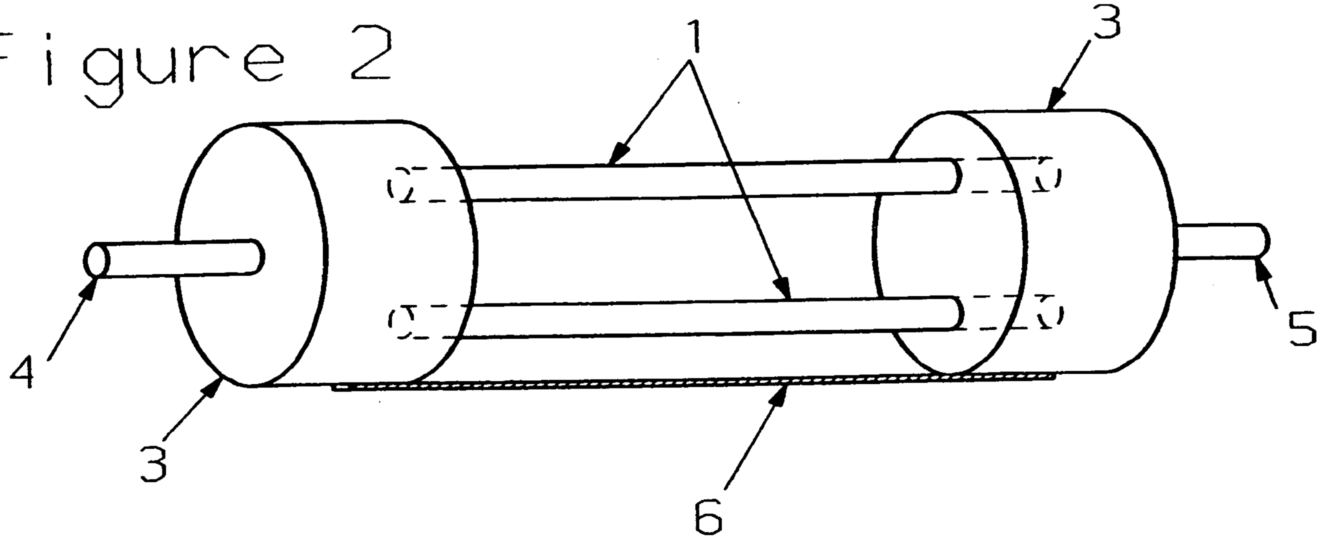
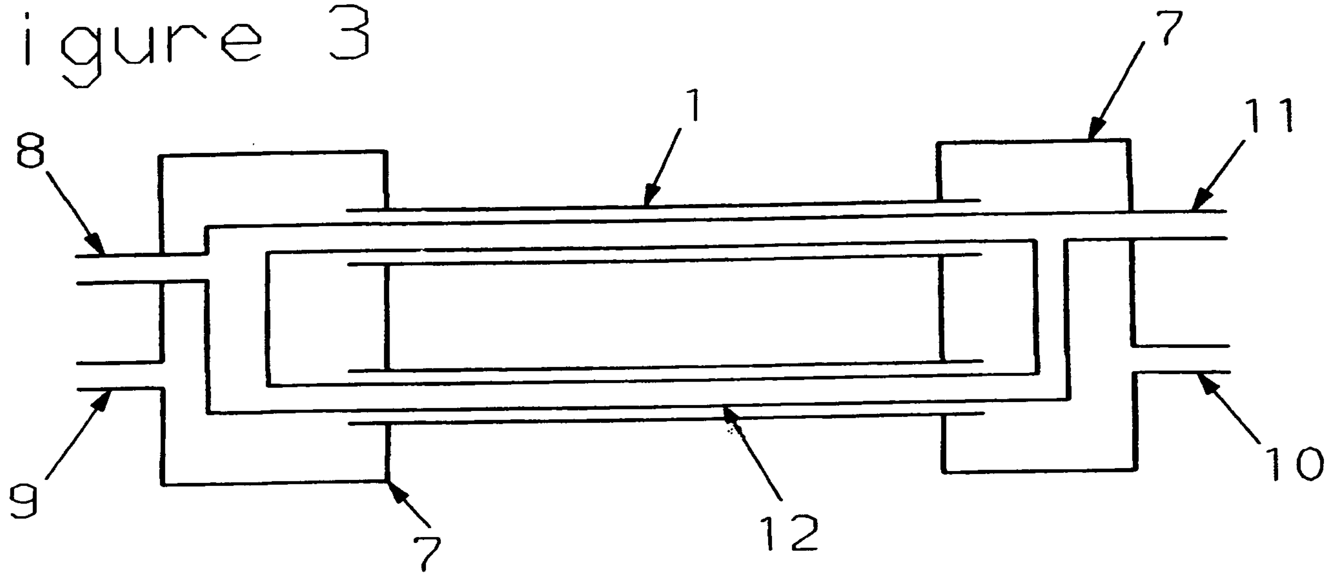


Figure 3



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